Canadian Patents Database

(12) **Patent:** (11) **CA 873873**

(54) PREPARATION OF ADAMANTANE-D16

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ABSTRACT
CLAIMS Show all claims

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(45)	Issued:	**1971-06-22**
(22)	Filed:	
(41)	Open to Public Inspection:	**1971-06-22**
(52)	Canadian Class (CPC):	**260/679.5 260/235.95**
(51)	International Class (IPC):	**N/A**
	Patent Cooperation Treaty (PCT):	**No**
(30)	Application priority data:	**None**
	Availability of licence:	**N/A**
	Language of filing:	**Unknown**

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Last updated: 2008-04-23

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This invention is concerned with the preparation of fully deuterated adamantane, that is adamantane-d_{16} which, itself, is a novel compound.

It was found, as one feature of this invention, that adamantane-d_{16} can be prepared by treating either endo or exo-tricyclo(5.2.1.0.^{2,6})decane with deuterium in the presence of a hydrogenation catalyst at a temperature from about ambient to 300° C. but preferably at about 250° C. The endo or exo-tricyclodecane-d_{16} (which also are new compounds) formed then can be isomerized to adamantane-d_{16} by treatment with a reagent capable of accepting electrons known in the profession as Lewis acids. The endo product is initially converted by this process to the exo-tricyclodecane and then to adamantane-d_{16} and can be carried out either in one step or in two.

The catalysts useful for exhange of endo or exo-tricyclodecane are to be found in the class known as hydrogenation catalysts which includes elements of Groups VI, VII and VIII of the periodic table, particularly these consisting of supported Group VIII metal catalysts and more specifically the platinum group which includes ruthenium, rhodium, palladium, osmium, iridium and platinum, although nickel catalysts also are useful. Catalyst supports other than carbon but chosen for their inertness and high surface area also can be employed. Diatomacious earth (kieselguhr), clay, alumina, and zeolites are some examples of commonly used supports.

Either liquid phase exchange or gas phase exchange can be employed for the purpose of deuterating the tricyclodecane. However, the gas phase exchange generally provides better yields of product of high isotopic and chemical

purity. Deuteration preferably is effected over a palladium-supported-on-carbon catalyst at a temperature of 250° C.

Preferred catalysts for the isomeration of the endo or exo-tricyclodecane-d_{16} to adamantane-d_{16} are aluminum chloride and aluminum bromide although other Lewis acid catalysts, such as FSO_3H-SbF_5 , also provide some yield of the desired product. Isomerization can be effected at a temperature ranging from about ambient temperature to 125°C.

Alternatively, as another feature of this invention, adamantane-d_{16} can be prepared by H-D exchange by admixing adamantane with a deuterated hydrocarbon, preferably n-dodecane-d_{26} or other activated deuterated hydrocarbons from which adamantane can readily be isolated, such as n-decane-d_{22}, n-hexadecane-d_{34}, n-octadecane-d_{38} and the like in the presence of a hydrogenation catalyst, especially elements of group VIII and more specifically the platinum group which include ruthenium, rhodium, osmium, iridium, platinum and palladium, in a sealed vessel.

The reaction does not need to be carried out under pressure although no disadvantage accrues to the use of a gas such as deuterium to pressurize the reaction vessel to any desired pressure. The vessel must be sealed however to prevent loss of adamantane by sublimation which will occur even at ambient temperature. Adamantane containing deuterium is recovered by cooling the hydrocarbon solution and filtering to remove the solid deuterated adamantane which upon repeated exchange of hydrogen by deuterium according to this process gives adamantane-d_{16}.

The H-D exchange advantageously is effected by shaking the reagents in the presence of the hydrogenation catalyst supported on any of the inert materials hereinbefore described at a temperature in the range of ambient to 300°C.

and advantageously at about 100° C.

Adamantane-d_{16} is useful in mass spectral analysis, in nuclear magnetic resonance studies and in radiolysis experiments.

The use of deuterated compounds as reagents follows from the fact that deuterated compounds undergo the same reactions as their nondeuterated analogues while modern analytical techniques distinguish between deuterium and hydrogen. Thus the fate of deuterium in reactions with deuterated compounds may be directly determined. Adamantane-d_{16} and its derivatives and exo-tricyclodecane-d_{16} would be useful for the determination of reaction mechanisms or the detailed description of how reagents are transformed into products and the factors affecting such transformations. Knowledge of reaction mechanisms is in turn helpful in the development of efficient, economical production processes.

Another example illustrating the assistance of deuterated compounds in chemical research is that of mass marking. Identification of mass spectral cracking fragments is facilited by subjecting both a deuterated compound and its undeuterated analogue to mass fragmentation. Fragments from the deuterated compound are shifted one mass unit higher per deuterium atom in the fragment than those from the undeuterated compound. In this way the number of deuterium (hydrogen) atoms in each fragment of the deuterated (undeuterated) compound can be determined. This information greatly simplifies the task of identifying each fragment.

Deuterated compounds such as adamantane-d_{16}, its derivatives, and exo-tricyclodecane-d_{16} also can be used as tracers in the study of separation processes and in combustion studies.

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Where resistance to decomposition by carbon-hydrogen bond rupture is required, deuterated compounds such as adamantane-d_{16}, its derivatives and exo-tricyclodecane-d_{16} can be employed because as is well known, more energy is required to rupture carbon-deuterium than carbon-hydrogen bonds. For example polymers based on adamantane-d_{16} can be expected to be less susceptible to oxidative and thermal degradation and thus better withstand extreme environments than nondeuterated analogues.

Solid, fully deuterated compounds are often used as targets in neutron diffraction studies. Adamantane-d_{16} is particularly useful for this purpose since large crystals of the compound can be prepared.

Deuterated derivatives of adamantane are also useful as metabolic tracers to study the metabolism of drugs containing the adamantane nucleus.

Adamantane-d_{16} is also a useful intermediate for preparing deuterated 1-amino adamantane, also known as amantadine, a product known to have antiviral properties particularly effective against influenza virus and measles virus. The deuterated amantadine additionally is useful in tracer studies of the activity of this compound against viral agents.

Adamantane-d_{16} can be converted by known procedures to fully deuterated 1-aminoadamantane-d_{15} by known methods which involve initially treating adamantane-d_{16} with bromine to provide the 1-bromo derivative. Reaction of the 1-bromo derivative with acetonitrile in the presence of sulfuric acid gives the 1-acetamido derivative which upon hydrolysis with base yields 1-aminoadamantane-d_{15}.

Other commercially useful derivatives of adamantane-d_{16} can be prepared such as 1-adamantanol-d_{15} which can be obtained from the 1-bromoadamantane-d_{15} upon treatment with silver nitrate and water in an organic solvent such as dioxane. Also, 1-adamantane-d_{15}-carboxylic acid can be obtained by the reaction of adamantane-d_{16} with a mixture of formic acid and sulfuric acid in tertiary butanol. These latter compounds are commercially useful in the study of separation processes and in combination studies.

The following examples will illustrate the novel methods for preparing adamantane-d_{16}. It will be obvious, of course, that modifications in the reaction conditions can be effected without departing from the spirit and scope of this invention.

EXAMPLE 1

Gas Phase Exchange

Step A: Preparation of exo-tricyclo[5.2.1.0.^{2,6}]decane-d_{16}

Exchange is effected by passing deuterium gas at the rate of 9 liters per hour through exo-tricyclodecane in an externally heated 200 ml. flask attached to the bottom of a vertical glass column containing 48 gm. (6%) palladium on carbon, 6-8 mesh, and heated to 250° C. In this way the mixture of deuterium gas and exo-tricyclodecane vapor is passed up through the catalyst bed where exchange is effected and the vapors led into a water cooled condensor arranged so as to permit the return by gravity of condensed exo-tricyclodecane to the flask at the bottom of the catalyst tower. One hundred grams of exo-tricyclodecane is charged into the bulb at the beginning of the run and 92.8 gm. (or 84 mole %) of substantially pure exo-tricyclodecane-d_{16} (99.1 atom % D)

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obtained after 195 hours of exchange.

The deuterium flow rate is not critical. Higher flow rates give faster exchange (less time required to reach 99% D) and lower flow rates give slower exchange.

Larger or smaller batch sizes can be used simply by increasing or decreasing the size of the flask used and, if desired, increasing or decreasing the amount of catalyst employed. Larger amounts of exo-tricyclodecane-d_{16} can also be prepared by connecting two or more runs as described in series or in parallel.

Step B: Preparation of adamantane-d_{16}

Exo-tricyclo(5.2.1.0.^{2,6})decane-d_{16} (25 g.) and aluminum chloride (25 g.) are heated at 65° C. for 19 hours with stirring during which period (at the end of 17 hours) deuterium oxide (1 ml.) is added. At the end of 19 hours, the reaction mixture is cooled in ice water, the aluminum chloride destroyed by quenching in a mixture of ice and water (H_2O), the hydrocarbon portion extracted with n-pentane, the pentane solution washed with distilled water, passed through a column of alumina for removal of colored impurities, dried over magnesium sulfate, filtered, and the n-pentane removed by flash evaporation to yield 22.4 g. of a pale yellow liquid-solid slurry. The slurry is cooled to -75° C. and filtered, yielding 9.45 g. of adamantane-d_{16} (98.9% D) containing 0.3% of unreacted starting material as the only impurity. Sublimation (50° C., 1-2 mm) gives a 96% yield (8.40 g.) of adamantane-d_{16} containing no detectable chemical impurities.

GKA. 6-V-70. N 6-V-70

EXAMPLE 2

Step A: Preparation of endo-tricyclodecane-d_{16}

25 g. Endo-tricyclo[5.2.1.$0^{2,6}$]decane put into a glass tube containing 6 g. 6% Pd/C, 6-8 mesh, which is then lowered into a 100° C. oil bath and D_2 gas flow at 100 ml/minute started. Twice a day material solidifying on the cool upper walls of the glass tube is melted and allowed to flow down into the bottom part of the tube. After 25 days of exchange endo-tricyclodecane-d_{16} is obtained.

Step A': Preparation of endo-tricyclodecane-d_{16} (98%D)

25 g. Endo-tricyclodecane is dissolved in a slight excess of an appropriate hydrocarbon such as n-dodecane and the resultant solution trickled at a rate of 80 drops per hour over 10 g. 6% Pd/C, 6-8 mesh, heated to 200° C. in the presence of deuterium gas passed through the catalyst bed cocurrent with the liquid feed at a rate of 9 liters per hour. A solution of endo-tricyclodecane (80%D) and n-dodecane (80%D) is obtained. Treating this material twice more under the same conditions gives a solution from which endo-tricyclodecane-d_{16} (98%D) is isolated in 50% yield by distillation or crystallization, with n-dodecane-d_{26} (98%D) as a by product.

Exchange is facilitated if a partially or completely deuterated hydrocarbon such as n-dodecane-d_{26} is used instead of n-dodecane. Valuable deuterated material may be conserved by reusing n-dodecane-d_{26} in subsequent preparations.

Step A'': Preparation of endo-tricyclo[5.2.1.$0^{2,6}$]decane-d_{16}

A saturated solution of endo-tricyclodecane in a suitable hydrocarbon such as n-dodecane-d_{26} is shaken with 6% Pd/C catalyst in a Parr hydrogenation bottle heated to 100° C. and connected to a Parr gas reservoir containing 30 p.s.i. D_2 gas. Shaking is continued for four (4) days then the catalyst removed by filtration, the solution is cooled and filtered yielding partially deuterated endo-tricyclodecane. Five further exchanges with n-dodecane-d_{26} by the above procedure provides endo-tricyclo[5.2.1.$0^{2,6}$]-decane-d_{16} ($\geq$98%D). A suitable sealed vessel such as a rocking autoclave from which air has been removed may be substituted for the Parr hydrogenation bottle and gas reservoir.

Step B: Preparation of adamantane-d_{16}

By replacing the exo-tricyclo[5.2.1.$0^{2,6}$]decane-d_{16} by the thus obtained endo-tricyclodecane-d_{16} and following substantially the same procedure described in Step B of Example 1 there is obtained adamantane-d_{16} in substantially the same isotopic purity.

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EXAMPLE 3

Liquid Phase Exchange

Step A: Preparation of exo-tricyclo(5.2.1.0.^{2,6})decane

Endo-tricyclo(5.2.1.0.^{2,6})decane (197 g.) and aluminum chloride (12 g.) are heated with stirring at 120° C. for three and three quarter hours. The yellow product formed is decanted from the aluminum chloride sludge and vacuum distilled to give exo-tricyclo(5.2.1.0.^{2,6})decane (177 g., 90% yield).

Step B: Preparation of exo-tricyclo(5.2.1.0.^{2,6})decane-d_{16}

Exo-tricyclodecane (6.69 g.) is trickled at the rate of 80 drops per hour over 6% Pd/C, 6-8 mesh (5 g.), heated to 147° C. in the presence of deuterium gas passed through the catalyst bed concurrent with the liquid feed at a rate of 4 liters per hour. Deuterated exo-tricyclodecane, 4.8 g. (82% D) is obtained. This material is treated twice more under the same conditions to give exo-tricyclodecane-d_{16} (98% D) in 30% overall yield.

A higher liquid to deuterium flow rate gives initial material of lower isotopic purity thus requring more recycles to reach 98% D whereas lower liquid/D_2 ratios give material of higher isotopic purity thus requiring fewer recycles to obtain 98% D material.

Step C: Preparation of adamantane-d_{16}

The exo-tricyclodecane-d_{16} obtained as described above is converted to adamantane-d_{16} by the same procedure described in Example 1, Step B.

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EXAMPLE 4

H-D Exchange Employing Deuterated Hydrocarbon

Adamantane-d_0 (6.5 g.) and n-dodecane-d_{26} (27 g.) are shaken with 6% palladium on carbon catalyst (20 g.) in a Parr hydrogenation bottle heated to 100° C. which is connected to a Parr gas reservoir containing 30 p.s.i. D_2 gas. After 4 hours additional n-dodecane-d_{26} (20 g.) is added and shaking continued for 4 days. After removal of the catalyst by filtration, the hydrocarbon solution is cooled and filtered yielding 3.0 g. adamantane of 44% D overall. Five further exchanges with n-dodecane-d_{26} by the above procedure provides adamantane-d_{16} ($\geq$ 98% D).

It should be noted that considerable adamantane remains in solution in n-dodecane when cooled. Maximum yields are obtained by adding more unexchanged adamantane to the deuterated n-dodecane/adamantane solution and exchanging again. This can be done with all the n-dodecane fractions obtained in the six step process thus cutting losses of valuable deuterated material to a minimum.

It was surprisingly found that adamantane-d_{16} can be converted to many useful substituted perdeutero adamantanes by conventional methods without isotope scrambling or dilution. In each case the isotopic purity of the adamantane nucleus of the derivative is identical to that of the adamantane-d_{16} starting material (97.7% D). Material of higher or lower isotopic purity may be used depending on the desired degree of isotopic purity in the adamantane derivative. Adamantane-d_{16} therefore can be employed to prepare derivatives containing the perdeutero adamantane nucleus using standard preparative techniques, and it additionally can similarly be used to prepare completely deuterated derivatives by reacting adamantane-d_{16} with appropriate

deuterated reagents.

Preparation of 1-bromo-adamantane-d_{15}

To adamantane-d_{16} (2.0 gm.) in a 100 ml. 3-neck flask fitted with water cooled condenser, dropping funnel, and magnetic stirrer and immersed in an oil bath at 30° C. is added, with stirring, bromine (5 ml.). Stirring is maintained and the bath temperature raised to 105° C. over four and one half hours. The reaction mixture is allowed to cool to room temperature, 20 ml. carbon tetrachloride added and the resulting solution poured into 60 ml. of water in a 250 ml. beaker. The two-phase mixture is cooled in an ice bath and sodium bisulfite added in small portions until the beaker contents are colorless (this serves to destroy residual bromine). The carbon tetrachloride layer is separated, washed with water, the water layer extracted with CCl_4, the CCl_4 layers combined, washed with 3 x 20 ml. water and dried over calcium chloride. The CCl_4 solution is filtered free of drying agent, CCl_4 removed by flash evaporation and the resultant crude yellow solid (3.23 gm.) recrystallized from hot methanol and sublimed (60° C, 1-2 mm.) to yield 1-bromoadamantane-d_{15}, 2.35 gm. (78 mole%), 98.8% D by n.m.r.

Preparation of 1-acetamidoadamantane-d_{15}

1-Bromoadamantane-d_{15} (0.80 gm) and acetonitrile (6 ml.) are placed in a 100 ml. flask fitted with dropping funnel and magnetic stirrer. After the bromoadamantane-d_{15} dissolves, 1.2 ml. concentrated H_2SO_4 is added dropwise with stirring and the reaction mixture stirred for a further 15 minutes then allowed to sit overnight (about 18 hours).

The resultant orange solution is poured into 20 ml. distilled water with consequent formation of a white precipitate which is collected by filtration. Neutralization of the filtrate with aqueous sodium hydroxide solution gives a small additional amount of precipitate. The yield is 0.64 gm (89%) of 1-acetamidoadamantane-d_{15} of 98% D (adamantane nucleus).

Preparation of 1-aminoadamantane-d_{15} ([redacted]amantadine-d_{15})

1-Acetamidoadamantane-d_{15} (0.50 gm.) is added to a hot solution of crushed sodium hydroxide (1 gm.) in diethylene glycol (10 ml.) and the resulting solution is refluxed for five and one half hours then cooled and poured into 25 ml. of water. The aminoadamantane-d_{15} so formed is extracted with several portions of ether, the ether layers combined and dried over KOH pellets, the dry ether solution filtered free of drying agent and evaporated to dryness. The resultant solid is sublimed (40° C., 1 mm.) to yield 1-aminoadamantane-d_{15} in 58% yield (0.23 gm.). Further purification is effected by passing dry HCl gas through an ether solution of the compound thus yielding the ether insoluble 1-aminoadamantane-d_{15} hydrochloride salt which is isolated by filtration. N.M.R. [redacted]. shows the adamantane nucleus of this compound to be 98% D.

Preparation of 1-adamantanol-d_{15}

A mixture of 1-bromoadamantane-d_{15} (0.617 gm.), dioxane (3 ml.), water (1 ml.), and silver nitrate (0.5 gm.) is refluxed for 3 hours in a 25 ml. flask fitted with a water cooled reflux condenser. The reaction mixture is then cooled, filtered, the filtrate diluted with water and flash

evaporated to dryness. The resultant solid is dried over $CaCl_2$ (in a dessicator) to yield 0.28 gm. of 1-adamantanol-d_{15} (63 mole %) of 98% D (adamantane nucleus).

Preparation of 1-adamantane carboxylic acid-d_{15}

Sulfuric acid (17.1 gm.; 95.5%), carbon tetrachloride (3.7 ml.) and adamantane-d_{16} (0.50 gm.) are added to a 100 ml. 3-neck flask fitted with a dropping funnel and magnetic stirrer. The reaction flask is lowered into a cooling bath, kept at 17-19° C. then two drops of formic acid (97-100%) added with vigorous stirring followed by the addition over 65 minutes of a solution of tertiary butanol (1.1 gm.) in formic acid (2 ml.) with the bath at 20-25° C. Stirring is continued for a further 40 minutes, the reaction mixture poured onto 25 gm. crushed ice, the upper acid layer extracted with 3 x 4 ml. carbon tetrachloride and the combined CCl_4 layers treated with 4 ml. of 15N ammonium hydroxide. The resultant precipitate is collected by filtration, washed with 1 ml. acetone (-75° C.) and then suspended in 10 ml. of water. The free acid is isolated by treatment of the water suspension with 1 ml. of 12N HCl, extraction with chloroform, drying of the chloroform solution over sodium sulphate, filtration to remove drying agent, and flash evaporation to remove solvent. The resultant solid is recrystallized from hot, 3/1, methanol/water to yield 0.32 gm. 1-adamantane-d_{15} carboxylic acid.

A small portion of this product is converted to the corresponding methyl ester by treatment with diazomethane. The adamantane nucleus of the methyl ester of 1-adamantane-d_{15} carboxylic acid is shown by mass spectrometry to have an isotopic purity of 98% D.

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Claims:

1. A process wherein endo or exo-tricyclo(5.2.1.0.^{2,6}) decane, D_2 gas and a hydrogenation catalyst are caused to react at between ambient to about 300° C. to provide the endo or exo-tricyclo(5.2.1.0.^{2,6})decane-d_{16} which optionally is isomerized at between about ambient and 125° C. in the presence of a Lewis acid to adamantane-d_{16}.

2. A process as claimed in Claim 1 wherein deuteration is carried out at a temperature of 250° C. in the presence of palladium on carbon.

3. A process as claimed in Claims 1 or 2 wherein isomerization is effected with a Lewis catalyst selected from aluminum chloride, aluminum bromide and FSO_3H-SbF_5.

4. Multiple H-D exchanges by combining in a reaction mixture adamantane and a deuterated hydrocarbon in the presence of a hydrogenation catalyst of group VIII elements at between about ambient to about 300° C. to provide adamantane-d_{16}.

5. A process as claimed in Claim 4 wherein the reaction mixture is heated at a temperature of about 100° C.

6. Adamantane-d_{16}.

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7. A perdeutero adamantane derivative selected from the group consisting of 1-bromoadamantane-d_{15}, 1-acetamido-adamantane-d_{15}, 1-aminoadamantane-d_{15}, 1-adamantanol-d_{15}, and 1-adamantane carboxylic acid-d_{15}.

8. Exo-tricyclo(5.2.1.0.^{2,6})decane-d_{16}.

9. Endo-tricyclo(5.2.1.0.^{2,6})decane-d_{16}.

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